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THE UTILITY OF PARTITION COEFFICIENTS IN DERMAL MODEL DEVELOPMENT FOR RAT AND GUINEA PIG

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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

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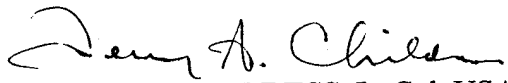

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The ability to extrapolate usable dermal penetration data from one species to another is fundamental to specific applications in risk assessment. The goal of this work is to quantitatively explain the movement of chemicals across the dermal barrier in differing species. The chemical absorbed during the exposure in amount per time per area ($mg/hr/cm^2$) is defined as the flux of the chemical. In order to estimate the total amount of chemical absorbed during the exposure, a physiologically-based pharmacokinetic (PBPK) model can be used if appropriate physiological and kinetic parameters are known. A primary data requirement of PBPK models is the partition coefficients for the chemical in blood and each of the tissue groups that display distinct kinetic behavior. In this study, blood, muscle, liver, and fat harvested from male Fischer 344 rats and male Hartley guinea pigs were exposed to four test chemicals. Using a vial equilibration method, the tissue:air partition coefficient was determined for Chloropentafluorobenzene (CPFB), 1,2-Dichlorobenzene (DCB), 1-Iodoheptafluoropropane (C_3F_7I) and Perfluorohexyl Iodide ($C_6F_{13}I$). The tissue:air partition coefficients generated in this study covered a four order magnitude range and were incorporated into PBPK models that were used for describing species differences in organic chemical absorption through the dermal barrier.

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PREFACE

The following research was conducted by the Tri-Service Toxicology Consortium. This research was accomplished as part of a larger project to determine species differences in dermal absorption kinetics of three test chemicals in three different species. The following research was accomplished from December 1993 to December 1994. Tissue:air partition coefficients were determined for Fisher 344 rats and Hartley Guinea pigs exposed to Chloropentafluorobenzene (CPFB), 1,2-Dichlorobenzene (DCB), 1-Iodoheptafluoropropane (C_3F_7I) and Perfluorohexyl Iodide ($C_6F_{13}I$).

The animals used in this study were handled in accordance with the principles in the Guide for Care and Use of Laboratory Animals, Institute of Health, Publication #86-23, 1985, and the Animal Welfare Act of 1966, as amended.

SECTION 1

INTRODUCTION

The use of physiologically-based pharmacokinetic (PBPK) modeling has been accepted by the scientific community as a reasonable means to simulate the kinetic behavior of chemicals in the animal system (Ramsey and Andersen ,1984). To accurately depict the chemical's behavior in the system, the system must be defined. To this end the simulation must identify those variables which are particular for a chemical in a specific species. Each species may have anatomical and physiological differences in behavior with regard to a chemical. One parameter which is particular to the species is the tissue:air partition coefficient, defined by the chemical's solubility into a particular tissue. The partition coefficient of a chemical is the unitless ratio achieved in the concentration of a chemical between two media at equilibrium (Gargas et al. 1989). The partition coefficient is further defined by the equation:

$$PC = \frac{(AC_{ref})(V_{vial}) - (AC_{sam})(V_{vial} - V_{sam})}{(AC_{sam})(V_{sam})} \quad \text{(eq. 1)}$$

The area counts for the reference and sample are AC_{ref} and AC_{sam}, respectively. V_{vial} and V_{sam} represent the volume in the vial and the volume of the sample, respectively. The PC described in equation 1 is an integral part of each biological tissue's description in a PBPK model. It has particular value in its ability to provide information about the distribution of chemical in biological tissues and systems.

This research examined the solubility of four chemicals into blood, muscle, liver and fat for two different species. Tissues taken from the Fisher 344 rat and the Hartley Guinea pig were exposed to CPFB, DCB, C_3F_7I and $C_6F_{13}I$. Data from this experiment was provided to other researchers for incorporation into PBPK models for each species. The iodinated compounds are of interest to the Air Force as candidates for non-ozone depleting aircraft fire extinguishers.

SECTION 2
METHODS AND MATERIALS

CHEMICALS

Chloropentafluorobenzene (CPFB)

Manufacturer	Aldrich Chemical Co., Milwaukee, WI
CAS#	344-07-0
Purity	99%
Molecular Formula	C_6ClF_5
Boiling Point (°C)	122

1,2-Dichlorobenzene (DCB)

Manufacturer	Aldrich Chemical Co., Milwaukee, WI
CAS#	95-50-1
Purity	99%
Molecular Formula	$C_6H_4Cl_2$
Boiling Point (°C)	180.40

1-Iodoheptafluoropropane (C_3F_7I)

Manufacturer	Flura Corporation, Newport, TN
CAS#	754-34-7
Purity	>99%
Molecular Formula	C_3F_7I
Boiling Point (°C)	40

Perfluorohexyl Iodide ($C_6F_{13}I$)

Manufacturer	Aldrich Chemical Co., Milwaukee, WI
CAS#	355-43-1
Purity	99%
Molecular Formula	$C_6F_{13}I$
Boiling Point (°C)	117

GAS CHROMATOGRAPH (GC) CONDITIONS

A Hewlett Packard 5890 Series II Gas Chromatograph with an electron capture detector (ECD) and a flame ionization detector (FID) was used in this study. Chloropentafluorobenzene (CPFB) partition coefficients (PC) were analyzed using an FID with a 10% SE-30 Chromosorb column (12'x1/8"). Column carrier flow was 30 mL/min. Hydrogen flow was 30 mL/min. Air flow was 300 mL/min. GC temperature conditions were optimized to 150°C oven, 150°C injector and 275°C detector. CPFB retention time on this column was 1.75 min. Partitions for DCB were analyzed using the ECD with DB-17 column (3m x 0.53cm). The GC flow was 5mL/min of 5% Argon/Methane and 45mL/min total flow. Oven temperature was 160°C with 200°C injector and 300°C detector temperature. Retention time for DCB was 6.7min. C_3F_7I data was analyzed using a flame ionization detector (carrier flow 13.4mL/min, hydrogen

flow 20mL/min, total flow 330mL/min) on a DB-17 column. The oven, injector and detector temperatures were 80, 125 and 300°C, respectively. Retention time for C_3F_7I was 0.7min. $C_6F_{13}I$ partitions were analyzed with FID and a 10% SE-30 Chromosorb column (12'x1/8"). Carrier flow was 30mL/min, Hydrogen flow was 30mL/min, and air flow was 300mL/min. Retention time for $C_6F_{13}I$ was 1.8min. Oven, injector and detector temperatures were 100, 125 and 250°C, respectively.

ANIMALS

Male Fisher 344 (F344) rats (150-400g) and Hartley Guinea pigs (400-750g) were obtained from Charles River Breeding Laboratory, Kingston, NY for use in this study. Prior to tissue harvest, animals were kept in a portable laminar air flow enclosure with a 12-hour on, 12-hour off light cycle. Animals had free access to commercial food and distilled-deionized water.

PROCEDURES

The tissue:air partitions described in this report were obtained using minced tissue in a modification of the vial equilibration technique described by Gargas et al. (1988). For each chemical detector response was quantified by standard curve.

Animal weights were recorded prior to euthanasia by 100% CO_2 . Blood, muscle, liver and fat tissues were then harvested from the subject animal. Blood was drawn by heparanized syringe and placed in a heparanized vacuum tube. The remaining tissues were harvested and chopped to obtain a near homogeneous sample while still leaving the tissue intact. For the exposures of CPFB, C_3F_7I and $C_6F_{13}I$, approximately 1 gram each of blood, muscle and liver were used to ensure a quantifiable loss. The high solubility of DCB into all tissues allowed use of a smaller sample while still exhibiting a quantifiable loss to the tissue. Approximately 0.1 gram of blood, muscle and liver was used in the DCB exposures. The amount of fat used varied by chemical. For CPFB, C_3F_7I and $C_6F_{13}I$, approximately 0.5 gram was utilized. The fat samples for DCB weighed 0.02 grams. The lighter weight was necessitated by the DCB's low volatility and high partition into fat. Three samples of each tissue were placed in a tared 12.67 mL Teflon-septum-sealed, glass vial. The sample weight was recorded. Time to equilibration studies were performed for each chemical and tissue type to ensure partitions were not analyzed prior to equilibration. Partitions were determined after a point where all tissues were at equilibrium. Harvested tissues were brought to

37°C by vortex evaporator. Once the tissues had incubated for 30min, 1mL of headspace was drawn from each sample. The sample vials were then injected with 1mL of volatilized chemical. The samples were incubated through the equilibration time point. At equilibrium 1 mL of the headspace was sampled from each vial and compared to reference vials of known concentration. The quantified detector response allowed for the calculation of the partition coefficient ratio

SECTION 3
RESULTS

CPFB, C_3F_7I and $C_6F_{13}I$ all exhibited a linear detector response for the exposure concentrations. The detector response for these three chemicals was linear in the range 0-400 ppm, vial concentration. The low volatility of DCB resulted in a very limited usable range of concentrations, 0-80 ppm, vial concentration. Detector response for DCB in this range was sigmoidal. Therefore, detector response to DCB concentration was quantified by a polynomial function for the exposure concentrations.

The time-to-equilibrium studies analyzed the tissue:air partition coefficients at 2, 3, 4 and 5 hour time points. The chemical was said to be at equilibrium when the partitioning ratio into the tissue no longer increased. Tissue:air partitions were analyzed when the chemical came to equilibrium with all tissue types. CPFB, DCB and C_3F_7I reached equilibrium at four hours. $C_6F_{13}I$ came to equilibrium at three hours.

Partition coefficient ratios for CPFB, DCB and $C_6F_{13}I$ were analyzed at different concentrations. Tissue:air partition coefficients were determined for each chemical at concentrations differing by one order of magnitude to ensure that the partition coefficients were not concentration dependent. The partition coefficient differences for these three chemicals into blood, muscle and liver at two different concentrations were not statistically significant, indicating no concentration dependence. $C_6F_{13}I$ did show a statistically significant difference in partitioning into rat blood at 40ppm versus 400 ppm. However, due to $C_6F_{13}I$'s low blood:air partition coefficient the statistics may be misleading in this case. The average blood:air PC at 40 ppm was 1.4 ± 0.3 while the blood:air PC at 400 ppm was 1.0 ± 0.1. For the same reason C_3F_7I partition coefficients were not run at different concentrations. The limited volatility of DCB coupled with its high fat partition did not allow for partitions at concentrations less than 40ppm in the vial. The fat:air partition coefficient of DCB, 26606 in rat and 10189 in pig, did however compare with the $15,657 \pm 703$ olive oil:air partition coefficient calculated from 15 exposures at 60 ppm DCB. The minimal loss of C_3F_7I and $C_6F_{13}I$ into blood, muscle and liver coupled with the extremely high PC of DCB into fat put analysis of these chemicals at the fringe of the volatile method's utility. The partitions coefficients given in tables 1-8 are averages of three samples for a given tissue in each animal.

TABLE 1

CPFB IN RAT (JEPSON ET AL. 1985)

TISSUE	PARTITION COEFFICIENT (MEAN)	STANDARD DEVIATION
BLOOD	13.5	0.5
MUSCLE	34.6	1.0
LIVER	30.6	0.5
FAT	766.0	16.4

TABLE 2

CPFB PARTITION COEFFICIENT (400 PPM) IN HARTLEY GUINEA PIG

ANIMAL #	WEIGHT (g)	TISSUE	PARTITION COEFFICIENT	**TISSUE AVERAGE**
#8	504.0	BLOOD	4.90 ± 0.14	
#9	514.5	BLOOD	5.75 ± 0.21	
#10	500.3	BLOOD	6.17 ± 0.35	
#11	540.9	BLOOD	5.23 ± 0.21	
#12	466.5	BLOOD	6.37 ± 0.15	**BLOOD**
#13	523.5	BLOOD	5.77 ± 0.06	5.70 ± 0.55
#8	504.0	MUSCLE	17.87 ± 1.25	
#9	514.5	MUSCLE	18.13 ± 1.53	
#10	500.3	MUSCLE	14.87 ± 5.40	
#11	540.9	MUSCLE	11.30 ± 1.42	
#12	466.5	MUSCLE	13.70 ± 1.51	**MUSCLE**
#13	523.5	MUSCLE	12.10 ± 0.56	14.66 ± 2.87
#8	504.0	LIVER	12.43 ± 2.93	
#9	514.5	LIVER	13.8 ± 1.55	
#10	500.3	LIVER	9.33 ± 0.25	
#11	540.9	LIVER	9.13 ± 0.57	
#12	466.5	LIVER	10.47 ± 0.42	**LIVER**
#13	523.5	LIVER	12.03 ± 2.61	11.20 ± 1.86
#8	504.0	FAT	654.73 ± 72.43	
#9	514.5	FAT	684.67 ± 48.20	
#10	500.3	FAT	570.77 ± 101.05	
#11	540.9	FAT	680.37 ± 44.09	
#12	466.5	FAT	711.80 ± 35.56	**FAT**
#13	523.5	FAT	600.07 ± 28.59	650.40 ± 54.29

*PARTITION COEFFICIENT DATA GIVEN AS MEAN OF 3 SAMPLES ± STANDARD DEVIATION

TABLE 3

DCB PARTITION COEFFICIENT (60 PPM) IN RAT

ANIMAL #	WEIGHT (g)	TISSUE	PARTITION COEFFICIENT	**TISSUE AVERAGE**
# 1	250	BLOOD	217 ± 8	
#38	389	BLOOD	246 ± 22	
#3	277	BLOOD	336 ± 8	**BLOOD**
#2	380	BLOOD	218 ± 14	254 ± 56
#1	250	MUSCLE	166 ± 39	
#38	389	MUSCLE	170 ± 46	
#3	277	MUSCLE	226 ± 36	**MUSCLE**
#2	380	MUSCLE	203 ± 10	191 ± 28
#1	250	LIVER	305 ± 49	
#38	389	LIVER	514 ± 100	
#3	277	LIVER	374 ± 69	**LIVER**
#2	380	LIVER	447 ± 50	410 ± 90
#1	250	FAT	21924 ± 1587	
#38	389	FAT	27238 ± 10751	
#3	277	FAT		**FAT**
#2	380	FAT	30655 ± 6443	26606 ± 4400

*PARTITION COEFFICIENT DATA GIVEN AS MEAN OF 3 SAMPLES ± STANDARD DEVIATION

TABLE 4

DCB (60 PPM) IN HARTLEY GUINEA PIG

ANIMAL #	WEIGHT (g)	TISSUE	PARTITION COEFFICIENT	**TISSUE AVERAGE**
#10	633	BLOOD	166 ± 5	
#8	581	BLOOD	144 ± 5	**BLOOD**
#5	742	BLOOD	141 ± 4	150 ± 14
#10	633	MUSCLE	186 ± 70	
#8	581	MUSCLE	163 ± 30	**MUSCLE**
#5	742	MUSCLE	162 ± 15	170 ± 14
#10	633	LIVER	328 ± 59	
#8	581	LIVER	332 ± 32	**LIVER**
#5	742	LIVER	269 ± 39	310 ± 35
#10	633	FAT	10205 ± 1032	
#8	581	FAT	10602 ± 637	**FAT**
#5	742	FAT	9761 ± 1035	10189 ± 421

*PARTITION COEFFICIENT DATA GIVEN AS MEAN OF 3 SAMPLES ± STANDARD DEVIATION

TABLE 5

C_3F_7I (400 PPM) IN RAT

ANIMAL #	WEIGHT (g)	TISSUE	PARTITION COEFFICIENT	**TISSUE AVERAGE**
#2	270	BLOOD	0.17 ± 0.2	
#3	319	BLOOD	0.40 ± 0.17	
#4	317	BLOOD	0.90 ± 0.17	
#6	314	BLOOD	0.43 ± 0.06	**BLOOD**
#9	299	BLOOD	0.80 ± 0.17	0.54 ± 0.30
#2	270	MUSCLE	0.76 ± 0.3	
#3	319	MUSCLE	0.77 ± 0.25	
#4	317	MUSCLE	0.43 ± 0.12	
#6	314	MUSCLE	0.43 ± 0.15	**MUSCLE**
#9	299	MUSCLE	0.13 ± 0.32	0.50 ± 0.27
#2	270	LIVER	0.33 ± 0.15	
#3	319	LIVER	-0.40 ± 0.17	
#4	317	LIVER	0.13 ± 0.12	
#6	314	LIVER	0.0	**LIVER**
#9	299	LIVER	0.03 ± 0.06	0.02 ± 0.27
#2	270	FAT	12.83 ± 3.38	
#3	319	FAT	9.37 ± 1.75	
#4	317	FAT	9.93 ± 0.76	
#6	314	FAT	11.43 ± 2.7	**FAT**
#9	299	FAT	12.50 ± 1.68	11.21 ± 1.53

*PARTITION COEFFICIENT DATA GIVEN AS MEAN OF 3 SAMPLES ± STANDARD DEVIATION

TABLE 6

C_3F_7I (400 PPM) IN GUINEA PIG

ANIMAL #	WEIGHT (g)	TISSUE	PARTITION COEFFICIENT	**TISSUE AVERAGE**
#4	586	BLOOD	1.2 ± 0.6	
#1	450	BLOOD	0.6 ± 0.3	
#2	425	BLOOD	0.1 ± 0.2	
#3	451	BLOOD	0.3 ± 0.2	**BLOOD**
#4	437	BLOOD	0.9 ± 0.3	0.6 ± 0.4
#4	586	MUSCLE	0.2 ± 0.1	
#1	450	MUSCLE	0.5 ± 0.2	
#2	425	MUSCLE	-0.03 ± 0.2	
#3	451	MUSCLE	0.3 ± 0.3	**MUSCLE**
#4	437	MUSCLE	0.2 ± 0.2	0.2 ± 0.2
#4	586	LIVER	0.2 ± 0.1	
#1	450	LIVER	0.3 ± 0.0	
#2	425	LIVER	0.3 ± 0.0	
#3	451	LIVER	0.2 ± 0.1	**LIVER**
#4	437	LIVER	0.3 ± 0.0	0.3 ± 0.1
#4	586	FAT	14.0 ± 2.7	
#1	450	FAT	11.0 ± 0.6	
#2	425	FAT	9.7 ± 4.2	
#3	451	FAT	5.1 ± 0.7	**FAT**
#4	437	FAT	4.0 ± 2.1	8.8 ± 4.2

*PARTITION COEFFICIENT DATA GIVEN AS MEAN OF 3 SAMPLES ± STANDARD DEVIATION

TABLE 7

$C_6F_{13}I$ (400 PPM) IN RAT

ANIMAL #	WEIGHT (g)	TISSUE	PARTITION COEFFICIENT	**TISSUE AVERAGE**
#1/#2 (pooled)	194/151	BLOOD	1.1 ± 0.1	
#3	184	BLOOD	0.6	
#5	179	BLOOD	0.9 ± 0.6	
#9	229	BLOOD	1.0 ± 0.1	**BLOOD**
#11	214	BLOOD	1.1 ± 0.1	0.94 ± 0.2
#1/#2 (pooled)	194/151	MUSCLE	1.3 ± 0.2	
#3	184	MUSCLE	1.0 ± 0.1	
#5	179	MUSCLE	1.0 ± 0.1	
#9	229	MUSCLE	0.9 ± 0.1	**MUSCLE**
#11	214	MUSCLE	1.0 ± 0.2	1.0 ± 0.2
#1/#2 (pooled)	194/151	LIVER	1.0 ± 0.2	
#3	184	LIVER	0.9 ± 0.1	
#5	179	LIVER	0.5 ± 0.1	
#9	229	LIVER	0.6 ± 0.1	**LIVER**
#11	214	LIVER	1.4 ± 0.5	0.9 ± 0.4
#1/#2 (pooled)	194/151	FAT	137.5 ± 1.1	
#3	184	FAT	114.3 ± 22.7	
#5	179	FAT	157.5 ± 7.9	
#9	229	FAT	115.3 ± 16.4	**FAT**
#11	214	FAT	128.5 ± 10.4	130.6 ± 17.9

*PARTITION COEFFICIENT DATA GIVEN AS MEAN OF 3 SAMPLES ± STANDARD DEVIATION

TABLE 8
$C_6F_{13}I$ (400 PPM) IN GUINEA PIG

ANIMAL #	WEIGHT (g)	TISSUE	PARTITION COEFFICIENT	**TISSUE AVERAGE**
#1	435.7	BLOOD	1.8 ± 0.4	
#2	421.5	BLOOD	1.0 ± .2	
#3	477.8	BLOOD	0.9 ± 0.1	
#4	487.2	BLOOD	1.2 ± 0.3	
#5	445.2	BLOOD	0.9 ± 0.2	**BLOOD**
#6	498.5	BLOOD	0.9 ± 0.1	1.2 ± 0.4
#1	435.7	MUSCLE	1.7 ± 0.0	
#2	421.5	MUSCLE	1.2 ± 0.1	
#3	477.8	MUSCLE	1.0 ± 0.2	
#4	487.2	MUSCLE	1.0 ± 0.2	
#5	445.2	MUSCLE	1.1 ± 0.1	**MUSCLE**
#6	498.5	MUSCLE	1.1 ± 0.1	1.2 ± 0.3
#1	435.7	LIVER	2.2 ± 0.6	
#2	421.5	LIVER	1.1 ± 0.0	
#3	477.8	LIVER	1.1 ± 0.2	
#4	487.2	LIVER	1.1 ± 0.1	
#5	445.2	LIVER	1.1 ± 0.0	**LIVER**
#6	498.5	LIVER	0.9 ± 0.2	1.3 ± 0.5
#1	435.7	FAT	8.4 ± 1.3	
#2	421.5	FAT	5.6 ± 0.9	
#3	477.8	FAT	6.1 ± 1.0	
#4	487.2	FAT	6.6 ± 2.0	
#5	445.2	FAT	8.4 ± 1.5	**FAT**
#6	498.5	FAT	8.5 ± 1.8	7.3 ± 1.3

*PARTITION COEFFICIENT DATA GIVEN AS MEAN OF 3 SAMPLES ± STANDARD DEVIATION

SECTION 3
DISCUSSION

In this study, the partition coefficients of four halogenated hydrocarbons (CPFB, DCB, C_3F_7I and $C_6F_{13}I$) were examined in blood, muscle, liver and fat of two different species, Fisher 344 rat and Hartley Guinea pig. The tissue:air partition coefficients of CPFB in the Hartley Guinea pig (blood:air = 5.70, muscle:air = 4.66, liver:air = 11.20 and fat:air = 650.40) were experimentally determined and compared well with earlier work described by Jepson et al. (1985). The minimal tissue partitioning seen in C_3F_7I and $C_6F_{13}I$ exposures resulted in the high coefficients of variation for blood:air, muscle:air and liver:air partition coefficients for these two chemicals. The marginal volatility of DCB drastically limited the range of exposure concentrations. The large partition numbers for DCB in all tissues, particularly fat (26,606 fat:air in Hartley Guinea pig) were also expected due to DCB's lipophilicity. Although, the chemicals used in this research are admittedly close to the useful limits of the analytical method used in this work, the research does have value in establishing qualitative and quantitative physiological parameters for the test chemicals.

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